Chapter 3

Schizophrenia syndromes in relation to executive and attentional function

Summary

In this article, we quantitatively review the published literature on the relationships between symptom dimensions in schizophrenia and performance on the two most widely applied tests of executive functioning and sustained attention, the Wisconsin Card Sorting Test and the Continuous Performance Test. Results of meta-analyses showed statistically significant relationships of negative symptoms with worse performance on the WCST (perseverations) and the CPT. Disorganisation symptoms correlated with perseverations on the WCST, but not with CPT performance. In contrast, reality distortion symptoms and general scores for all positive symptoms did not correlate with either measure. However, the observed associations between psychiatric symptoms and cognitive performance were typically weak, suggesting relative independence of these disease processes.

Introduction
Deficits in executive functioning and vigilance are considered core neurocognitive abnormalities in schizophrenia (Randolph et al., 1993; Green, 1998). Impaired performance on the most widely applied neuropsychological tests of executive functioning and vigilance, the Wisconsin Card Sorting Test and the Continuous Performance Test, respectively, has been associated with psychosis-proneness (Franke et al., 1992; Nelson et al., 1998) and worse functional outcome (Green and Nuechterlein, 1999; Harvey et al., 1999). Although patients with schizophrenia have often been reported to perform worse than normal controls on these tests a recent quantitative review indicated that these differences may be attributed to a subgroup of patients (Heinrichs and Zakzanis, 1998). Since performance on both tests has been associated with deficits of prefrontal functioning, these findings suggest the existence of a subtype of schizophrenia in which pathology of the neural networks involving the frontal lobes is most pronounced (Zakzanis and Heinrichs, 1999). Following Crow's two syndrome hypothesis (Crow, 1980), many researchers have adopted a symptom-based approach in attempting to identify the dimensions along which these patients may be discerned from others (e.g. Liddle, 1987).

Executive functions involve such abilities as abstract reasoning, concept formation, decision making and planning of behavior. Based on a rule learning paradigm which invokes these abilities the Wisconsin Card Sorting Test (WCST; Milner, 1963) has been one of the most widely applied neuropsychological measures of executive functioning (Heaton, 1993). Although schizophrenic patients have consistently been shown to perform worse than normal controls on the WCST (Heinrichs and Zakzanis, 1998), research relating WCST performance to symptom dimensions has produced inconsistent results. Some authors reported findings indicating that predominantly negative symptoms are related to poor performance (Addington et al., 1991; Berman et al., 1997; Perry and Braff, 1998; Rosse et al., 1993). Others, however, have failed to replicate this finding (Cuesta et al., 1995; Himelhoch et al., 1996; Ragland et al., 1996). The relation of WCST performance to positive symptomatology is even less clear, with findings indicating relations varying from better (e.g. Hammer et al., 1995) to worse (e.g. Perry and Braff, 1998) performance on the WCST. However, the positive dimension of schizophrenia symptomatology has been shown to be heterogeneous, with accumulating findings suggesting the subdivision of positive symptomatology into symptoms of disorganisation and reality distortion (Liddle,
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It has been argued that disorganisation symptoms may be strongly related to multiple cognitive deficits, whereas reality distortion symptoms such as hallucinations and delusions have been associated with relatively intact cognitive functioning (Green, 1998).

The CPT is a well-known measure of vigilance, which refers to sustaining attention on a stimulus or a certain dimension of that stimulus over a period of time (Nuechterlein et al., 1994). The typical variable measured is the decrement in signal/noise discrimination within the vigilance period, termed sensitivity. Poor performance on the CPT has been identified as a vulnerability marker to schizophrenia (Nuechterlein et al., 1994), thereby suggesting performance to be independent of clinical state. Nuechterlein’s contention has been supported by Cornblatt et al.’s failure to find significant relations between CPT performance and either positive or negative symptoms (Cornblatt et al., 1997). Others, however, have suggested an important role of impaired attention in the genesis of positive symptoms and psychosis in general (Nelson et al., 1998; Berman et al., 1997; Addington et al., 1997). Finally, findings have also been reported that CPT impairment is related to negative symptoms (Strauss, 1993).

There are two factors that may have contributed to the inconsistencies in reported associations between symptom dimensions and neuropsychological test performance. First, the studies that report these relations differ with respect to the clinical state of the studied patients. Specifically, some studies concern acute schizophrenic patients (eg. Addington et al., 1991), whereas other studies included only chronic patients (eg. Liddle et al., 1991). Baxter and Liddle (1998) have suggested that associations between symptoms dimensions and performance on neuropsychological tests may differ for patients in different phases of the illness. Second, methodological differences may contribute to the inconsistencies in reported associations. Specifically, the use of different symptom scales such as the BPRS, SANS and PANSS may result in different correlations between cognitive deficits and clusters of symptoms that were derived from these scales through factor-analysis.

The aim of the present study was to provide a quantitative review of the literature on symptom dimensions and performance on the WCST and CPT. By performing a meta-analysis on all studies in this domain, we investigated the validity of claims about differential relations between symptom dimensions and cognitive deficits (Crow, 1980; Green, 1998). In addition, the use of meta-analysis enables an evaluation of the role of between-study differences in sample
characteristics and symptom scales in accounting for the inconsistencies in reported associations.

**Method**

**Literature search** Articles for consideration were identified through an extensive literature search in the Psychlit and Medline databases, from 1980 through December 1999. The key words were: “schizophrenia and executive functions”, “schizophrenia and Wisconsin*”, “schizophrenia and WCST”, “schizophrenia and sustained attention”, “schizophrenia and continuous*” and “schizophrenia and CPT”. In order to minimize the possibility of overlooking studies due to the limited purview of computer databases we paged through the volumes of relevant journals published in 1999. The selection of journals was based on the frequency of the publication of relevant articles. The journals included American Journal of Psychiatry, Biological Psychiatry, Journal of Nervous and Mental Disease, Psychiatry Research, Schizophrenia Bulletin and Schizophrenia Research. The search produced over 250 unique studies from which titles and abstracts were examined for possible inclusion in our analysis.

**Criteria for inclusion** The identified studies were included if they met the following criteria. First, the study had to include patients with a diagnosis of schizophrenia (based on DSM, ICD or RDC criteria). Studies that also included patients with schizoaffective or schizotypal disorders were excluded if the data on schizophrenic patients were not reported separately. Second, each study had to include valid measures of symptomatology. Measures included were: Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983), the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984), the positive and negative component scales of the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) and the positive and negative component scales of the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962). In addition, we included studies that computed scores for clusters of symptoms based on factor-analyses of the SANS, SAPS, PANSS and BPRS scales. These studies often included descriptive statistics for measures of reality distortion and disorganisation subsyndromes, thereby enabling meta-analysis of the relation with WCST and CPT performance. From studies reporting correlations for separate symptoms we computed scores for the
disorganisation, negative, positive and reality distortion dimensions by averaging the scores for symptoms constituting these dimensions. Third, the studies had to report valid measures of the Wisconsin Card Sorting Task (Heaton et al., 1993) or the Continuous Performance Task (Nuechterlein and Dawson, 1984). We included perseverative errors, perseverative responses and the number of categories completed as WCST performance measures. Factor-analytical findings indicate that these variables load on a factor termed perseveration (PE) which has been reported to differentiate well between schizophrenic patients and normals (Cuesta et al., 1995; Koren et al., 1998). When a study reported separate correlations between symptom dimensions and multiple WCST variables we computed the pooled effect size. The measure of the Continuous Performance Task included for meta-analysis was the measure of sensitivity, d'. If selected studies presented measures for different experimental conditions (e.g. neuroleptic naive versus neuroleptic free) we computed a pooled effect size. Fourth, the studies had to report correlational statistics, which are suitable for meta-analysis by providing direct measures of the relation between scores on scales of symptomatology and neuropsychological test performance. Finally, the population samples from the studies included had to be independent.

For the WCST meta-analysis 16 studies that met the criteria could be included, whereas 6 studies were included in the CPT meta-analysis (studies included in the analyses are marked with an asterisk in the reference list). Tables 1 and 2 list sample and study characteristics of the studies included in the WCST and CPT meta-analyses, respectively.

Data collection and analysis. We performed meta-analyses on the correlational data reported in the selected studies. Analyses were performed on relations of negative, positive, disorganisation and reality distortion symptomatology with the CPT measure of sensitivity, d', and WCST-PE. From studies reporting measures of multiple versions of the CPT we selected results for the versions that most resembled the CPT paradigm developed by Nuechterlein and Dawson (Nuechterlein and Dawson, 1984).

For computation of population effect sizes we used mean r-values weighted for sample size (Hunter, Schmidt, & Jackson, 1982; Hunter & Smidt, 1990). The combined r-value is an indication of the strength of associations across all selected studies. The corresponding z-value and significance level provide an indication of the significance of the association.
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For WCST-PE, a positive correlation indicated an association between symptomatology and worse performance, whereas for the CPT variable d', positive correlations indicated that more symptoms were associated with better performance. In addition we calculated a $\chi^2$ statistic for an indication of the heterogeneity of results across studies in a single category (Hunter et al., 1982; Rosenthal, 1991). A significant $\chi^2$ statistic indicates that the observed variance in study effect sizes is significantly greater than would be expected by chance if all studies shared a common population effect size. Thus, if homogeneity is rejected, the mean weighted r-value should not be interpreted as an estimate of a single effect parameter that gave rise to the sample observations, but rather simply as describing a mean of observed effect sizes, which of course limits a reliable interpretation and generalization. If there is significant heterogeneity, categorical moderator analyses may be performed by grouping studies into appropriate categories until homogeneity is not rejected within those categories. In the present context, heterogeneity would signify the role of possible confounding factors such as phase of illness.

Analyses were performed using the statistical software package META (Schwarzer, 1988).

**Results**

As can be seen in table 3, negative and disorganisation symptoms correlated significantly with WCST-PE ($r=0.27$ and $r=0.25$, respectively, both $p's <0.01$). The magnitude of the correlations is small to modest, in the nomenclature of Cohen (1988). Composite scores for all positive symptoms and the cluster of reality distortion symptoms did not correlate with WCST-PE. Vigilance performance measured with CPT-d' only correlated with negative symptoms, $r=-0.31$, $p<0.01$. Associations of total positive symptoms on one hand, or disorganisation and reality distortion on the other hand, with either WCST or CPT performance were not significant. As can be seen in table 3, there was no significant heterogeneity of effect sizes within the analyses. Although the results failed to indicate significant heterogeneity, we performed additional analyses using the sample and study characteristics listed in Tables 1 and 2 as moderator variables. None of these analyses reached significance.
Table 3. Results of meta-analyses on all studies for WCST-perseveration and CPT-d'

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dimension</th>
<th>N</th>
<th>k</th>
<th>r</th>
<th>Z</th>
<th>95% CI</th>
<th>(\chi^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WCST</td>
<td>Negative</td>
<td>699</td>
<td>15</td>
<td>0.27</td>
<td>7.23*</td>
<td>0.13 - 0.40</td>
<td>18.9</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>487</td>
<td>9</td>
<td>0.06</td>
<td>1.24</td>
<td>-0.15 - 0.27</td>
<td>13.3</td>
</tr>
<tr>
<td></td>
<td>Disorganisation</td>
<td>273</td>
<td>6</td>
<td>0.25</td>
<td>4.22*</td>
<td>0.24 - 0.26</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>Reality distortion</td>
<td>194</td>
<td>4</td>
<td>0.04</td>
<td>0.60</td>
<td>-0.22 - 0.30</td>
<td>7.4</td>
</tr>
<tr>
<td>CPT</td>
<td>Negative</td>
<td>250</td>
<td>6</td>
<td>-0.31</td>
<td>-4.94*</td>
<td>-0.41 - -0.21</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>188</td>
<td>4</td>
<td>-0.01</td>
<td>-0.10</td>
<td>-0.10 - 0.09</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>Disorganisation</td>
<td>98</td>
<td>2</td>
<td>-0.06</td>
<td>-0.54</td>
<td>-0.04 - -0.08</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>Reality distortion</td>
<td>98</td>
<td>2</td>
<td>0.04</td>
<td>0.39</td>
<td>0.02 - 0.06</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*\(p<0.01; k=number of studies; N=total number of subjects; r=mean weighted correlation; Z=Stouffer’s Z for significance of effect size; 95\%CI=95\% confidence interval; \(\chi^2\)=heterogeneity between studies

**Discussion**

The goal of the present study was to provide a quantitative review of the relations between dimensions of schizophrenia symptoms and performance on neuropsychological tests of executive functioning and vigilance. Negative symptoms were significantly associated with impairments in both domains of cognitive functioning. In contrast, general scores for all positive symptoms and separate scores for reality distortion symptoms were not associated with either WCST or CPT performance. Disorganisation symptoms showed a significant correlation with worse WCST performance, but not with CPT performance. The observed significant correlations were in the small to modest range. In addition, these relations were shown to be stable across studies that differed in sample and study characteristics.
The present results confirm the existence of differential, albeit weak, relations between the symptom dimensions of schizophrenia and deficits in executive functioning and vigilance (Baxter and Liddle, 1998; Liddle, 1996; Strauss, 1993). These differential syndrome-cognition relations can be linked to evidence showing that different anatomical structures are associated with the negative, positive and reality distortion syndromes of schizophrenia. Results from brain imaging studies have demonstrated that negative symptoms are associated with abnormalities of the frontal cortex (Andreasen et al. 1998; Schröder et al. 1996). Our observation of significant relationships between negative symptoms and impaired performance on neuropsychological tests that have been associated with frontal lobe functioning is in accordance with these neuroanatomical findings. Disorganisation symptoms have been shown to have similar relations with frontal lobe functioning (Crider, 1997; Liddle et al., 1992). In contrast, reality distortion symptoms have been associated with abnormalities of the temporal lobes (Liddle et al., 1992; Kaplan et al., 1993; Wright et al., 1995).

The present findings address two important issues regarding the use of syndrome-based approaches in the study of cognition in schizophrenia. First, the fact that disorganisation and reality distortion showed differential relations with neurocognitive performance supports the notion that positive symptoms do not form a homogeneous syndrome (Liddle, 1987). Indeed the fact reality distortion symptoms did not correlate with WCST nor CPT performance, whereas disorganisation did correlate with WCST performance, is in agreement with findings from several factor-analytical studies of schizophrenia symptoms which have shown that these symptoms constitute a distinct dimension of schizophrenia symptoms (see Grube et al., 1998, for a meta-analysis). Taken together, these findings favor a three syndrome model over the two syndrome model as proposed by Crow (1980).

A second issue concerns the degree to which these syndromes can account for heterogeneity in performance on neuropsychological tests. Although we found significant associations between some symptom dimensions and performance on the WCST and the CPT, the magnitude of the weighted mean correlations indicated that these dimensions account for less than 10% of the variance in performance on these tests. Taken together with the observed differential nature of the correlations, this suggests that, although symptom dimensions and their neurocognitive correlates may be remotely related to a common pathophysiological alteration, they do not necessarily co-occur across
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the time-course of schizophrenia. This interpretation is in agreement with the model of schizophrenia recently proposed by Green and Nuechterlein (1999). According to this model, neurocognitive deficits are central to the chronic disabilities of patients with schizophrenia and relatively independent of symptomatic expressions of schizophrenia. Indeed, neurocognitive deficits have been shown to be more closely related to the schizophrenia genotype than symptomatic expressions, with several findings indicating the presence of cognitive deficits both before the onset and throughout the course of schizophrenia (Goldberg et al., 1993; Green and Nuechterlein, 1999), as well as in schizotypic relatives of schizophrenic patients (Franke et al., 1992; Nelson et al., 1998). Conversely, symptomatic expressions fluctuate considerably across the time-course of schizophrenia (Carpenter et al., 1988; Murray, 1997), with negative symptoms constituting relatively enduring traitlike characteristics (Arndt et al., 1995). Cognitive deficits and negative symptoms may thus both reflect a trait-like pathophysiology in schizophrenia.

In conclusion, the present study provides some evidence for the hypothesis that dimensions of schizophrenia symptoms may be distinctly related to neurocognitive function. Negative symptoms and disorganisation symptoms show associations with impaired performance on neuropsychological tests sensitive to frontal functioning, whereas reality distortion symptoms do not. By obtaining differential correlations between symptom dimensions and neurocognitive performance, to a certain extent our meta-analysis can be taken to support the external validity of the symptom-dimensions model. However, the association between symptoms and neurocognition must not be overstated. The present findings of relatively weak correlations seem to favor a model of schizophrenia in which symptom dimensions and performance on classical neuropsychological tests are relatively independent (Green & Nuechterlein, 1999). This is not to say that cognitive functioning may not act as intermediate level between phenomenology (symptoms) and neurobiology, as has been proposed by Mortimer & McKenna (1994). However, fine-grained studies with experimental tasks aimed at specific cognitive processes in relation to individual symptoms may have more explanatory power than relating syndromes to classical neuropsychological tests (which are typically involve more than one cognitive process). Without doubt, however, the understanding of the heterogeneous features of schizophrenia is likely to benefit importantly from further elaboration
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of the neurocognitive basis of distinct clinical phenomena characteristic of this disabling condition.
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(Studies included in meta-analysis are indicated with an asterisk)


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